RISK OF LEUKEMIA AFTER PLATINUM-BASED CHEMOTHERAPY FOR OVARIAN CANCER

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ABSTRACT

Background Platinum-based chemotherapy is the cornerstone of modern treatment for ovarian, testicular, and other cancers, but few investigations have quantified the late sequelae of such treatment.

Methods We conducted a case–control study of secondary leukemia in a population-based cohort of 28,971 women in North America and Europe who had received a diagnosis of invasive ovarian cancer between 1980 and 1993. Leukemia developed after the administration of platinum-based therapy in 96 women. These women were matched to 272 control patients. The type, cumulative dose, and duration of chemotherapy and the dose of radiation delivered to active bone marrow were compared in the two groups.

Results Among the women who received platinum-based combination chemotherapy for ovarian cancer, the relative risk of leukemia was 4.0 (95 percent confidence interval, 1.4 to 11.4). The relative risks for treatment with carboplatin and for treatment with cisplatin were 6.5 (95 percent confidence interval, 1.2 to 36.6) and 3.3 (95 percent confidence interval, 1.1 to 9.4), respectively. We found evidence of a dose–response relation, with relative risks reaching 7.6 at doses of 1000 mg or more of platinum (P for trend <0.001). Radiotherapy without chemotherapy (median dose, 18.4 Gy) did not increase the risk of leukemia.

Conclusions Platinum-based treatment of ovarian cancer increases the risk of secondary leukemia. Nevertheless, the substantial benefit that platinum-based treatment offers patients with advanced disease outweighs the relatively small excess risk of leukemia. (N Engl J Med 1999;340:351-7.)

CISPLATIN and carboplatin are among the most important drugs introduced during the past three decades for the treatment of cancer. These derivatives of platinum have a central role in chemotherapy for patients with cancers of the ovary, testis, bladder, lung, endometrium, and head and neck. The platinum compounds, however, are carcinogenic in vitro and in laboratory animals,[1] producing intrastrand and interstrand DNA cross-links in a manner similar to that of bifunctional alkylating agents.[2] The development of leukemia in patients treated with platinum-based chemotherapy has been noted in case reports,[1] but few analytic studies have estimated the risk of leukemia after such treatment. Quantification of the late effects of platinum is especially important for women with ovarian cancer, since the optimal therapeutic approaches, including preferred drug doses, continue to be defined.[3]

Ovarian cancer is the second most common gynecologic cancer in the United States, with an estimated 25,400 cases in 1998.[4] Because survival after a diagnosis of ovarian cancer has improved greatly within the past two decades,[5] the late sequelae of treatment have assumed increasing clinical importance.[6] We report our evaluation of the risk of leukemia after therapy for ovarian cancer among 28,971 women who were treated in North America and Europe during the 1980s and 1990s.

METHODS

Patients

We conducted a case–control study of secondary leukemia in a cohort of 28,971 women with invasive ovarian cancer reported to population-based cancer registries[7] in Connecticut, Iowa, New Jersey, Ontario, Denmark, Finland, and Sweden. Eligibility criteria for the cohort included the diagnosis of a first primary cancer of the ovary between January 1, 1980, and December 31, 1993 (the dates varied slightly according to the registry, with an end date of December 31, 1991, in Connecticut, New Jersey, and Denmark; December 31, 1992, in Ontario and Sweden; and December 31, 1993, in Finland and Iowa), and survival for at least one year. For each patient, registry data were searched to identify all subsequent diagnoses of leukemia or the myelodysplastic syndrome. Chronic lymphocytic leukemia was not included, since it has not been linked to prior radiotherapy or chemotherapy. To identify other blood dyscrasias that might represent myelodysplastic syndrome, we searched mortality files, as well as hospital-discharge records in Denmark, Finland, and Ontario, to find patients with ovarian cancer who had an underlying cause of death or a discharge diagnosis of severe anemia or another blood disorder. For all reported secondary hematologic cancers, clinicopathological data, including reports of bone marrow aspirations and biopsies, were reviewed to confirm eligibility for the study. The 96 eligible patients, identified from cancer-incidence files (83 pa-

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tients) or the other sources noted above (13), included 90 patients with acute myeloid leukemia or myelodysplastic syndrome, 3 with acute lymphoblastic leukemia, and 3 with chronic myeloid leukemia. For simplicity, all these diagnoses are subsequently referred to as leukemia.

For each patient with leukemia, three control patients were chosen by random sampling from the defined cohort, with a 2:1 ratio used for cases from the New Jersey registry. The control patients were matched for registry, age when ovarian cancer was diagnosed, year of diagnosis of ovarian cancer, and survival without a second primary cancer for at least as long as the interval between the case patient's diagnoses of ovarian cancer and leukemia.

Data Abstracted from Medical Records

For each patient, standardized forms were used to collect demographic and clinical data, including information on all treatment for ovarian cancer during the matched time period. Sources of data included medical centers, local hospitals, radiotherapy facilities, and offices of private physicians. Information on the dose and duration of treatment was collected for platinum, all alkylating drugs, doxorubicin, and the epipodophyllotoxins. For other cytotoxic drugs, abstracted data were limited to dates and duration of treatment. Information on cumulative dose was available from medical records for 98 percent of patients (96 percent of the patients with leukemia and 98 percent of the control patients) included in the dose–response analyses; for the other 2 percent, the cumulative dose was estimated on the basis of the duration of therapy or was imputed from the median dose administered. Daily radiotherapy logs for each patient were used to calculate doses of radiation to 17 sections of active bone marrow, according to methods described elsewhere,[8] with doses weighted and summed to obtain an overall mean value.

Statistical Analysis

Conditional logistic regression was used to estimate the relative risk of leukemia associated with specific therapies by comparing the exposure history of each patient with secondary leukemia with that of the individually matched controls.[9,10] This analytic approach, with exposure expressed in terms of the absolute dose of the cytotoxic drug, has been used in previous studies of secondary leukemia.[11-13] Women were grouped into mutually exclusive treatment categories according to total history of chemotherapy, based on either the platinum compound or most frequently used alkylating drugs. Because platinum derivatives and bifunctional alkylating drugs produce DNA cross-links,[2] they were grouped together for the initial analyses.[14] Since the leukemogenicity of cyclophosphamide is known to be weak[11-13,15] at the low cumulative doses frequently used in chemotherapeutic regimens for ovarian cancer, patients who received this drug in addition to melphalan or platinum were categorized in terms of the latter drugs. Additional analyses were conducted to adjust for doses of cyclophosphamide and doxorubicin. Patients were considered to have been exposed to an alkylating drug or platinum if they had received it for one or more months. Comparisons between treatment categories were based on likelihood-ratio tests. Two-sided P values and 95 percent confidence intervals were computed. The results of analyses performed with and without cases identified by mechanisms other than registry records were not significantly different from one another.

Estimates of the dose–response relation between specific drugs and the risk of leukemia were calculated by dividing patients into subgroups according to even increments of the cumulative dose of the drug (or the duration of therapy) and calculating the relative risk of leukemia for each subgroup as compared with the group of patients who had not been exposed to alkylating drugs or platinum (the reference group). For the platinum category, carboplatin doses were divided by 4 to convert them to cisplatin-equivalent doses.[16] Tests for trend were conducted by assigning the midpoint of the cumulative dose or duration of therapy to be the representative score for that category.[9] The excess number of cases of leukemia among 10,000 patients with ovarian cancer followed for 10 years was estimated with the use of previously described methods.[13]

TABLE 1. CHARACTERISTICS OF WOMEN WITH SECONDARY LEUKEMIA AND MATCHED CONTROL PATIENTS AMONG 28,971 PATIENTS TREATED FOR OVARIAN CANCER.

CHARACTERISTIC	PATIENTS WITH LEUKEMIA (N=96)	CONTROL PATIENTS (N=272)*
	no. (%)†	
Registry		
Connecticut	11 (11)	33 (12)
Denmark	3 (3)	9 (3)
Finland	9 (9)	27 (10)
Iowa	15 (16)	45 (17)
New Jersey	11 (11)	22 (8)
Ontario	24 (25)	72 (26)
Sweden	23 (24)	64 (24)
Age at diagnosis of ovarian cancer		
<50 yr	10 (10)	30 (11)
50–59 yr	18 (19)	55 (20)
60–69 yr	40 (42)	106 (39)
≥70 yr	28 (29)	81 (30)
Year of diagnosis of ovarian cancer		
1980–1984	57 (59)	156 (57)
1985–1989	31 (32)	92 (34)
1990–1993	8 (8)	24 (9)
Stage of ovarian cancer		
I or II	40 (42)	186 (68)
III or IV	56 (58)	86 (32)
Period of latency‡		
<2 yr	20 (21)	56 (21)
2–4 yr	49 (51)	138 (51)
5–9 yr	24 (25)	68 (25)
≥10 yr	3 (3)	10 (4)
Treatment§		
No radiotherapy or alkylating drugs¶	5 (5)	58 (21)
Radiotherapy but no alkylating drugs	1 (1)	36 (13)
Alkylating drugs but no radiotherapy	65 (68)	135 (50)
Radiotherapy and alkylating drugs	25 (26)	43 (16)

*Controls were matched for registry, age, year of diagnosis of ovarian cancer, and period of latency (see the Methods section).

†Percentages may not sum to 100 because of rounding.

‡The period of latency was the interval between the diagnosis of ovarian cancer and that of leukemia for the patients with leukemia, with a comparable interval for the matched controls.

§Because platinum compounds produce intrastrand and interstrand DNA cross-links[2] that are similar to those formed by bifunctional alkylating drugs, they were considered together for the initial analyses.[14]

¶This category includes 5 patients with leukemia and 58 controls who underwent surgery without treatment with alkylating drugs or radiotherapy.

RESULTS

Most of the women in our study were over 60 years old when they received a diagnosis of ovarian cancer; 42 percent were treated during the mid-1980s or later (Table 1). On average, secondary leukemia developed 4 years (median, 3.3; maximum, 13.7) after the diagnosis of ovarian cancer. A larger proportion of patients with leukemia (94 percent) than control patients (65 percent) were treated with alkylating drugs or platinum. Among the women given alkylating drugs or platinum, 66 percent of the patients with secondary leukemia (59 of 90) and 72 percent of the controls (128 of 178) achieved clinical remission, with treatment for relapse subsequently administered to 8 and 16 women, respectively. Seventy-one of all 96 patients with secondary leukemia (74 percent) were in clinical remission at the time of the diagnosis of leukemia; the subsequent median survival of these women was three months. The median dose of radiation to active bone marrow was 13.4 Gy (range, 1.5 to 20.9) for the patients with leukemia and 15.7 Gy (range, 0.6 to 25.6) for the controls, with an average dose of 42 Gy to the tumor.

Patients who received alkylating drugs or platinum without radiotherapy had a relative risk of leukemia of 6.5 (95 percent confidence interval, 2.3 to 18.5), as compared with the women in the reference group, who received neither alkylating drugs nor radiotherapy. With combined-mode therapy, the relative risk was 8.1 (95 percent confidence interval, 2.6 to 25.6) (Table 2). Patients who received radiotherapy (median dose, 18.4 Gy) without cytotoxic drugs did not have an increased risk of leukemia; however, most of our patients did not receive radiotherapy.

Patients treated with chemotherapy most often received platinum (28 percent of the patients with leukemia and 38 percent of the controls), melphalan (29 percent of the patients with leukemia and 15 percent of the controls), or both (20 percent of the patients with leukemia and 6 percent of the controls). Platinum derivatives were frequently given in combination with cyclophosphamide, doxorubicin, or both. The patients with leukemia received a median of nine cycles of cisplatin or seven cycles of carboplatin, with median cyclical doses of 90 mg and 520 mg, respectively. Women in the control group received a median of seven cycles of cisplatin or six cycles of carboplatin, with median cyclical doses of 50 mg and 500 mg, respectively. The median duration of platinum treatment was 9.9 months (range, 4.7 to 37.2) for the patients with leukemia and 7.5 months (range, 1.0 to 36.8) for the controls. When melphalan was administered, it was usually the sole drug given. Only eight women received chlorambucil or treosulfan. Epipodophyllotoxins were given to only two women, both in the control group. No patients received paclitaxel.

The risk of leukemia was significantly increased after treatment with platinum (relative risk, 4.0; 95 percent confidence interval, 1.4 to 11.4) but was considerably lower than the risk after treatment with melphalan (relative risk, 20.8; 95 percent confidence interval, 6.3 to 68.3) (Table 3). Among patients treated with both platinum and melphalan, the relative risk of leukemia was 31.5 (95 percent confidence interval, 8.9 to 111.1). Too few women received other alkylating drugs alone to estimate the associated risks separately.

Table 4 shows the relative risk of leukemia accord-

TABLE 2. RISK OF LEUKEMIA ASSOCIATED WITH ALKYLATING DRUGS AND RADIOTHERAPY.

TREATMENT*	PATIENTS WITH LEUKEMIA	MATCHED CONTROL PATIENTS	RELATIVE RISK (95% CI)†
	no.		
No alkylating drugs or radiotherapy	5	58	1.0
Radiotherapy but no alkylating drugs	1	36	0.4 (0.04–3.5)
Alkylating drugs but no radiotherapy	65	135	6.5 (2.3–18.5)
Alkylating drugs and radiotherapy	25	43	8.1 (2.6–25.6)

*Alkylating drugs included platinum derivatives.

†Patients who received neither alkylating drugs nor radiotherapy were the reference group. CI denotes confidence interval.

TABLE 3. RISK OF LEUKEMIA ACCORDING TO THE TYPE OF ALKYLATING DRUG.

TREATMENT*	PATIENTS WITH LEUKEMIA	MATCHED CONTROL PATIENTS	RELATIVE RISK (95% CI)†
	no.		
Platinum‡	27	103	4.0 (1.4–11.4)
Melphalan§	28	40	20.8 (6.3–68.3)
Platinum and melphalan¶	19	15	31.5 (8.9–111.1)
Other alkylating drugs alone‖	7	9	8.1 (2.0–33.5)
More than one alkylating drug**	9	11	14.0 (3.6–54.6)

*Treatment categories were mutually exclusive. Alkylating drugs were usually given in combination with other drugs.

†The reference group consisted of 6 patients with leukemia and 94 controls who were not exposed to platinum derivatives or other alkylating drugs. CI denotes confidence interval.

‡Patients in this category received therapy with a platinum derivative as the principal alkylating drug. Other cytotoxic drugs administered included doxorubicin (in 6 patients with leukemia and 14 controls), cyclophosphamide (in 11 patients with leukemia and 47 controls), or both (in 10 patients with leukemia and 36 controls). The cumulative dose of cyclophosphamide was less than 10,000 mg in 73 percent of patients with leukemia and 89 percent of controls.

§Patients in this category received therapy with melphalan as the principal alkylating drug. Doxorubicin was administered to 5 patients with leukemia and 12 controls. The remaining patients (23 patients with leukemia and 28 controls) received no other cytotoxic drugs.

¶Therapy frequently included multiple courses, during which patients received a platinum derivative or melphalan or both.

‖This category included three patients with leukemia and one control who were treated with chlorambucil, two patients with leukemia and two controls treated with treosulfan, one patient with leukemia and six controls given cyclophosphamide, and one patient with leukemia treated with a single alkylating drug that was not specified.

**Patients in this category received two or more of the following cytotoxic drugs: platinum, melphalan, altretamine (hexamethylmelamine), mitomycin, chlorambucil, carboquone, and ifosfamide. Patients who received platinum and melphalan without other alkylating drugs were included in the third category listed.

ing to the cumulative dose of platinum, the duration of therapy, and the specific platinum agent for patients who did not receive melphalan. The relative risks of leukemia after cumulative doses of less than 500 mg, 500 to 749 mg, 750 to 999 mg, and 1000 mg or more of platinum were 1.9, 2.1, 4.1, and 7.6, respectively (P for trend <0.001). A multivariate model that adjusted for the cumulative amount of cyclophosphamide and doxorubicin did not provide a better fit for the data (P=0.66) than a model that took into account only categories of cumulative platinum doses. The risk of leukemia increased with the duration of platinum-based chemotherapy, with a relative risk of 7.0 among women who were treated for more than 12 months (P for trend=0.001). The relative risk of leukemia was 3.3 (95 percent confidence interval, 1.1 to 9.4) after cisplatin-based regimens and 6.5 (95 percent confidence interval, 1.2 to 36.6) after carboplatin-based regimens.

Patients who received radiotherapy and platinum-based chemotherapy had a significantly higher risk of leukemia than those who received platinum alone (P=0.006) in a multivariate model adjusted for cumulative amount of drug. There was a dose–response relation for platinum among both women who received radiotherapy and those who did not, with a higher risk in the radiotherapy group (which included 8 patients with leukemia and 15 controls); in all 23 of these patients, radiotherapy was administered as part of the initial treatment. The overall risk of leukemia for patients who received platinum-based chemotherapy and radiotherapy was 12.2 (95 percent confidence interval, 3.1 to 47.5).

The risks of leukemia after platinum-based chemotherapy were 2.4, 3.8, and 5.6, respectively, less than 2 years, 2 to 4 years, and 5 or more years after the diagnosis of ovarian cancer (range, 1.3 to 7.0 years). Although the risk of leukemia associated with platinum-based treatment tended to be somewhat higher among younger patients, differences according to age were not significant (P value for heterogeneity, 0.48; data not shown). For each registry, the risk of leukemia was three to seven times as high for women who received platinum-based treatment as for the reference group (P for heterogeneity=0.31), with higher risks at centers that administered radiotherapy.

Since women given melphalan without platinum for ovarian cancer received all drugs entirely by intravenous or oral administration, we were able to examine the effect of the route of administration and the dose on the risk of leukemia (Table 5). There was a significantly increased risk of leukemia after intravenous administration of melphalan (relative risk, 22.9) and after oral administration (relative risk, 9.0), and the risk increased with increases in the cumulative dose and the duration of therapy (Table 5). These relative risks were not increased among women who also received radiotherapy (P=0.58 for oral melphalan and P=0.37 for intravenous melphalan).

TABLE 4. RISK OF LEUKEMIA ACCORDING TO THE CUMULATIVE DOSE OF PLATINUM, DURATION OF THERAPY, AND SPECIFIC DRUG.*

DOSE AND DURATION	PATIENTS WITH LEUKEMIA	MATCHED CONTROL PATIENTS	MEDIAN VALUE IN CONTROLS†	RELATIVE RISK (95% CI)‡
	no.			
All platinum drugs				
Dose§				
<500 mg	4	30	418 mg	1.9 (0.5–7.9)
500–749 mg	5	28	600 mg	2.1 (0.6–8.0)
750–999 mg	7	25	896 mg	4.1 (1.1–14.8)
≥1000 mg	11	20	1230 mg	7.6 (2.3–25.3)¶
Duration				
<6 mo	3	36	5.4 mo	1.2 (0.3–5.5)
6–12 mo	16	49	8.5 mo	4.3 (1.4–12.9)
>12 mo	8	18	14.2 mo	7.0 (1.8–26.6)‖
Specific drug				
Cisplatin	19	85	600 mg	3.3 (1.1–9.4)
Carboplatin	3	9	3300 mg	6.5 (1.2–36.6)
Both	5	9		9.0 (2.2–37.6)
Cisplatin			720 mg	
Carboplatin			2200 mg	

*The data are limited to 27 patients with leukemia and 103 controls who received platinum-based chemotherapy without melphalan.

†The values shown are median cumulative doses of platinum and the median duration of therapy among controls.

‡The reference group consisted of 6 patients with leukemia and 94 controls who were not exposed to platinum derivatives or other alkylating drugs. CI denotes confidence interval.

§Cumulative amounts of carboplatin were divided by 4 to convert them to cisplatin-equivalent doses.[16]

¶P for trend <0.001.

‖P for trend=0.001.

DISCUSSION

We found that the risk of leukemia was significantly increased after treatment with platinum-based chemotherapy for ovarian cancer. The magnitude of the risk depended on the cumulative dose of the drug and the duration of treatment. In addition, the risk of leukemia was significantly higher among the small number of patients who received both platinum and radiotherapy. Our findings, based on a follow-up study of 28,971 women with ovarian cancer, may be applicable to the treatment of other patients with cancer, including those with cancer of the testis, lung, head and neck, endometrium, or bladder, who often receive treatment with platinum derivatives. In 1998, cancers at these sites were diagnosed in approximately 325,000 patients in the United States.[4] A proportion of these patients may have been eligible for platinum-based chemotherapy with or without radiotherapy.

Platinum compounds are the cornerstone of current treatment for ovarian cancer. There are conflict-

TABLE 5. RISK OF LEUKEMIA ACCORDING TO THE CUMULATIVE DOSE OF MELPHALAN, DURATION OF THERAPY, AND ROUTE OF ADMINISTRATION.*

DOSE AND DURATION	PATIENTS WITH LEUKEMIA	MATCHED CONTROL PATIENTS	MEDIAN VALUE IN CONTROLS†	RELATIVE RISK (95% CI)‡
	no.			
Intravenous melphalan	17	25	140 mg	22.9 (4.6–112.0)
Dose				
<250 mg	9	19	130 mg	13.5 (2.5–73.0)
≥250 mg	8	6	319 mg	64.7 (8.8–477.0)§
Duration				
<12 mo	10	21	4.2 mo	14.9 (2.7–80.8)
≥12 mo	7	4	14.0 mo	127.7 (10.6–1543.0)¶
Oral melphalan	11	15	440 mg	9.0 (2.7–30.0)
Dose				
<500 mg	4	11	425 mg	5.6 (1.3–24.4)
≥500 mg	7	4	950 mg	26.2 (5.7–121.0)§
Duration				
<12 mo	4	11	11.1 mo	5.5 (1.3–23.7)
≥12 mo	7	4	24.2 mo	32.7 (6.3–170.0)§

*The data are limited to 28 patients with leukemia and 40 controls who received melphalan without platinum. Each patient received melphalan entirely by intravenous or oral administration. Intravenous melphalan was administered at a median dose of 25 mg once a month to both patients with leukemia and controls (number of cycles in patients with leukemia: median, 6.5; mean, 9.4; range, 1 to 19; number of cycles in controls: median, 4.0; mean, 5.5; range, 2 to 19). With oral formulations of melphalan, a median daily dose of 10 mg was given five days per month to both patients with leukemia and controls (number of cycles in patients with leukemia: median, 12.0; mean, 12.3; range, 8 to 18; number of cycles in controls: median, 10.0; mean, 10.2; range, 4 to 20). Five patients with leukemia and 12 controls who received intravenous melphalan also received doxorubicin. No other cytotoxic drugs were given to the women who received oral formulations of melphalan.

†The values shown are median cumulative doses of melphalan and the median duration of therapy among controls.

‡The reference group consisted of 6 patients with leukemia and 94 controls who were not exposed to platinum derivatives or other alkylating drugs.

§P for trend <0.001.

¶P for trend <0.001.

ing data, however, on the optimal dose and combination of cytotoxic drugs, duration of therapy, and choice of platinum compound.[17,18] Kaye et al.[3] recently estimated that the preferred dose of cisplatin may be 75 mg per square meter of body-surface area given every three weeks for six cycles, which amounts to a cumulative dose of 765 mg for the average woman (body-surface area, 1.7 m^2). The women in our study received a wide range of platinum doses, permitting an evaluation of the risk of leukemia over a broad spectrum of cumulative amounts. Since epipodophyllotoxins were not administered to these patients, it was possible to evaluate the carcinogenicity of platinum apart from that of etoposide, which is known to increase the risk of leukemia.[19] Paclitaxel, which in combination with platinum represents the current standard of care for patients with advanced ovarian cancer, was not used in our study and, to our knowledge, has not been identified as a leukemogen in animals or humans.

The dose-dependent leukemogenicity of platinum that we observed is consistent with the observation that in patients given cisplatin-based therapy, the concentration of cisplatin–DNA adducts increases as a function of the drug dose and is correlated with the clinical response to therapy.[20] If our findings are confirmed, it will be especially important to weigh any therapeutic benefit derived by increasing the dose of platinum against the risk of subsequent leukemia. The risk–benefit considerations may be especially important for women with early-stage ovarian cancer,[21] who accounted for 42 percent of the patients with secondary leukemia in our series.

Our finding that radiotherapy may increase the carcinogenicity of platinum-based chemotherapy is noteworthy in view of therapeutic strategies designed to maximize the dose intensities of both modes of treatment.[22,23] Although it is unlikely that women who receive a diagnosis of ovarian cancer in the late 1990s will receive both platinum and radiotherapy, in the light of recent treatment recommendations,[21] the possibility that the risk of leukemia after treatment with platinum is increased by radiotherapy should be investigated among patients with other cancers, especially cancers of the testis, bladder, and head and neck.

In our study, intravenous melphalan was found to be almost six times as leukemogenic as platinum. The lower risk associated with platinum should reassure patients and clinicians; indeed, current recommendations[21] do not include the use of intravenous melphalan for ovarian cancer, and platinum and melphalan are usually not used together. Nevertheless, the leukemogenic potential of high cumulative doses of intravenous melphalan is disturbing, especially when the drug is used in children with relapsed neuroblastoma or as salvage therapy in adults with Hodgkin's disease or cancer of the breast or ovary.[24] In our study, oral administration of melphalan was considerably less leukemogenic than intravenous administration, a finding that seems consistent with the variable systemic bioavailability of the drug and less pronounced myelosuppressive effects after oral administration.[24]

The risk of leukemia after chemotherapy for Hodgkin's disease has been studied extensively.[25] The median time to the diagnosis of leukemia and the dose–response relation with the combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) are similar to our findings after platinum-based chemotherapy. However, the overall relative risk of MOPP-associated leukemia, which may reach 60 to 80 at high doses,[25] is substantially greater than the risk we observed after platinum-based chemotherapy for ovarian cancer. Most studies show that radiotherapy given alone for Hodgkin's disease confers either no increase in the risk of leukemia or only a small increase[25] — a finding similar to ours for ovarian cancer (but based on relatively few patients). In the largest study of Hodgkin's disease to date,[26] radiotherapy did not appear to add to the risk of leukemia associated with chemotherapy. However, this issue remains open to considerable debate.[25]

Pivotal, unanswered questions are whether other drug combinations that include platinum are associated with similarly increased risks of leukemia, whether such risks are enhanced by radiotherapy, and how host factors, such as variations in drug excretion and DNA repair, influence these risks. It will also be important to determine whether platinum-based chemotherapy is associated with excess solid tumors. The persistence of platinum–DNA adducts in numerous human tissues, including kidney and brain tissue (as well as bone marrow), long after treatment has been completed[27] heightens the concern about late effects. Furthermore, platinum causes solid tumors, as well as leukemia, in laboratory animals.[1] Possible interactions between platinum compounds and radiotherapy in the development of solid tumors will be especially important to evaluate among long-term survivors of testicular cancer for whom the risk of a second cancer increases steadily with time.[28] Oral formulations of platinum,[29] which also enhance the cell-killing effects of radiotherapy,[30] are now being developed. The possible carcinogenic effects of these new agents must be clarified, with the development of approaches that will minimize these risks.

Among 10,000 women with ovarian cancer who are treated for 6 months with a cumulative dose of 500 to 1000 mg of cisplatin or more than 1000 mg and then followed for 10 years, an excess of 21 and 71 cases of leukemia, respectively, might be expected on the basis of our data. Before the advent of platinum-based treatment, only about 40 percent of patients with advanced ovarian cancer had responses to therapy, the median survival was one year, and only a small percentage of patients survived for at least five years.[31] With platinum-based therapy, such patients have a clinical response rate of 60 to 70 percent, with a survival rate of up to 20 to 30 percent at five years.[21,31] Thus, in balancing the risks and benefits of platinum-based chemotherapy for the treatment of ovarian cancer, it is clear that the substantial improvements in survival far outweigh the relatively small excess risk of secondary leukemia.

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